Reliable Generation of Induced Pluripotent Stem Cells From Human Lymphoblastoid Cell Lines.

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Funding Grants: Use of iPS cells (iPSCs) to develop novels tools for the treatment of spinal muscular atrophy.

Public Summary:
In Barrett et al. we developed a novel method to re-create motor spinal motor neurons and intestinal stem cells from patients who died decades ago. Using stored blood samples create pluripotent stem cells, termed iPS cells; we can more easily study the potential causes of debilitating illnesses such as spinal muscular atrophy (SMA) and inflammatory bowel disease (IBD).This research could yield new therapies for people who suffer from aggressive motor-neuron and gut-related conditions that proved fatal to the deceased patients who long ago volunteered their blood samples. By using a deceased patient's stored blood samples, we found that they we can efficiently develop stem cells known as iPSCs in a petri dish – essentially reanimating diseased cells from patients long after they have passed away. The technique also allows physicians to replace invasive biopsy procedures typically required of living patients to create iPSC cells. These developments allow us to create new lines of stem cells and their affected cell types from literally millions of patient samples stored in large repositories, including SMA, a devastating and often fatal childhood neurological disease. In this study we also show that these recreated stem cells can efficiently make diseased cells from patients, i.e. neurons specific to the spine (motor) for a SMA patient as well as cells of the gut from healthy subjects. Since it is very difficult to get unlimited access to study affected cells and tissues from the patients, our discoveries now allow us such important capabilities. Thus, now we are not limited to animal models of disease, but can use these patient-specific stem cells to better pinpoint potential causes of these devastating illnesses. Using these patient iPS cells developed from blood, we recreated millions of motor neurons that are affected in SMA. This technology now provides us with better systems to screen for thousands of candidate drugs on multiple SMA patients. In addition, this approach will allow us in the future to connect the dots between a deceased a patient's symptoms, genetic information contained in DNA and the behavior of diseased cells created in our labs. By now having the ability to create large numbers of the diseased cell types, we are now correlating the clues from the behaviors of these cells in a dish to the large wealth of knowledge gained previously from the genetic studies. This will ultimately help us design better drugs.

Scientific Abstract:
Patient-specific induced pluripotent stem cells (iPSCs) hold great promise for many applications, including disease modeling to elucidate mechanisms involved in disease pathogenesis, drug screening, and ultimately regenerative medicine therapies. A frequently used starting source of cells for reprogramming has been dermal fibroblasts isolated from skin biopsies. However, numerous repositories containing lymphoblastoid cell lines (LCLs) generated from a wide array of patients also exist in abundance. To date, this rich bioresource has been severely underused for iPSC generation. We first attempted to create iPSCs from LCLs using two existing methods but were unsuccessful. Here we report a new and more reliable method for LCL reprogramming using episomal plasmids expressing pluripotency factors and p53 shRNA in combination with small molecules. The LCL-derived iPSCs (LCL-iPSCs) exhibited identical characteristics to fibroblast-derived iPSCs (fib-iPSCs), wherein they retained their genotype, exhibited a normal pluripotency profile, and readily differentiated into all three germ-layer cell types. As expected, they also maintained rearrangement of the heavy chain immunoglobulin locus. Importantly, we also show efficient iPSC generation from LCLs of patients with spinal muscular atrophy and inflammatory bowel disease. These LCL-iPSCs retained the disease mutation and could differentiate into neurons, spinal motor neurons, and intestinal organoids, all of which were virtually indistinguishable from differentiated cells derived from fib-iPSCs. This method for reliably deriving iPSCs from patient LCLs paves the way for using invaluable worldwide LCL repositories to generate new human iPSC lines, thus providing an enormous bioresource for disease modeling, drug discovery, and regenerative medicine applications.

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